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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/420,692	10/19/1999	JEFFREY M. BESTERMAN	106.101.197	3139

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EXAMINER	
EPPS FORD, JANET L	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/420,692	BESTERMAN ET AL.	
	Examiner	Art Unit	
	Janet L. Epps-Ford, Ph.D.	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6 and 11-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6 and 11-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11-14-03 has been entered.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

3. Claims 1-3, 6, and 11-34 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting the expression of a gene in a cell *in vitro* and in xenograft tumor cells in an experimental mouse model *in vivo* does not reasonably provide enablement for inhibiting the expression of a gene *in vivo* for the therapeutic treatment of mammals broadly, an in particular a human, having a disease associated with the expression of said gene. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for the reasons of record set forth in the Official Action mailed 5-08-02.

4. Applicant's arguments filed 11-14-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification enables one skilled in the art to make and/or use the invention commensurate in scope with the claims. According to Applicants, the test of enablement is not whether any experimentation is necessary,

but whether, if experimentation is necessary, it is undue. Moreover, Applicants argue that as long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement is satisfied. Additionally, Applicants argue that the experimental data set forth in the 1.132 Declaration filed 1-15-2003, provides sufficient evidence to demonstrate that one of ordinary skill in the art recognizes that a mouse model is a generally accepted model for humans.

Contrary, to Applicant's assertions neither Applicant's arguments nor the Declaration filed 1-15-03, provide sufficient evidence that the specification as originally filed enables the full scope of the claimed invention. As stated in the prior Office Action, the Declaration provided by Applicants, which provides experimental data describing the administration of a single antisense oligonucleotide, the contents of the Declaration is not commensurate in scope with the claimed invention, which is directed to the co-administration of antisense oligonucleotides with an effective synergistic amount of a DNA MeTase protein effector.

The Declaration of 1-15-2003 does not address the issue of the DNA MeTase protein effector. The claimed invention requires the co-administration of an "effective synergistic amount" of a protein effector of undefined structure. The ordinary skilled artisan would have to resort to trial and error experimentation in order to find an appropriate protein effector of DNA MeTase that would function in a synergistic manner with a co-administered antisense, since neither the specification as filed nor the Declaration of 1-15-2003 provide sufficient guidance to practice this aspect of the claimed invention. Therefore, the contents of the Declaration of 1-15-03 do not provide a reasonable correlation to the entire scope of the claimed invention.

The instant claims are not limited to any particular antisense oligonucleotide sequence; therefore the claims encompass the administration of any antisense oligonucleotide targeting DNA MeTAse, in combination with a of undefined structure protein effector. As stated previously, although the data provided in the Declaration may enable the in vivo use of MG98, the results obtained using that particular inhibitor cannot be extrapolated in order to predict the behavior of all antisense inhibitors of DNA MeTase *in vivo,* or to predict the structure and behavior of a protein effector co-administered with an antisense inhibitor. As stated in the prior Office Action, since Crooke (1998) clearly teaches that there are a significant number of factors that influence the behavior of antisense based compounds in a cell, one of skill in the art would not accept on its face that the data supporting the use of MG98 would be necessarily predictive of the use of other antisense compounds targeting DNA MeTase, and further with the co-administration of a protein effector.

Applicant's arguments are not persuasive, the instant claims remain rejected for the reasons of record.

5. Claims 1-3, 6, and 11-34 remain rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in the Official Action mailed. 5-8-02.

Applicant's arguments filed 11-14-03 have been fully considered but they are not persuasive. Applicants traverse the instant rejection on the grounds that the specification as filed satisfies the written description requirement. Moreover, Applicants argue that the specification

teaches how to design antisense oligonucleotides to human DNA methyltransferase, teaches how to determine if the antisense oligonucleotides inhibit the expression of human DNA methyltransferase and discloses how to administer a therapeutically effective synergistic amount of said antisense oligonucleotides and a protein effector to a human for the purpose of treating disease and/or inhibiting tumor growth. Applicants refer to the arguments previously made, and submit that one skilled in the art would recognize that the inventors had possession of the claimed invention at the time the application was filed. Applicant's arguments to support the written description of the antisense oligonucleotides targeting human DNA MeTase appear to be based upon further experimentation using the specification as filed as a guide.

See the January 5, 2001 (Vol. 66, No. 4, pages 1099-1111) Federal Register for the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement. These guidelines state: "[T]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention."

Applicants are describing the claimed invention by describing a method for isolating the

claimed invention. However, a description of a method for obtaining a functional antisense oligonucleotide or protein effector, and further providing a description of their function is insufficient to provide an adequate written description of an invention since neither the prior art nor the specification as filed provides any correlation between the structure of the structure of the claimed invention and its function. See MPEP § 2163[R-1].I.A. which states, "The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence."

Furthermore, in regards to the protein effectors useful in the claimed methods, Applicant's own work, clearly state that the "[D]irect evidence that elevated DNA MeTase levels alter gene expression and influence oncogenesis has been difficult to obtain, in part due to the lack of specific DNA MeTase inhibitors." Moreover, Applicants state that most work related to the experimental inhibition of DNA MeTase has relied upon for the most part on the nucleoside analogs 5-azacytidine and 5-azadeoxycytidine. Applicants make no reference to any known structure of any other protein effectors that are effective to inhibit the activity of DNA MeTase, Applicants also note that the activity of 5-azacytidine and 5-azadeoxycytidine are not specific from DNA MeTase (see Fournel et al. August 1999, page 24250, paragraph 1 and abstract). It is noted that the instant application has an effective filing date of 10/19/1998 since it claims

priority to provisional application 60/104,804. Even after the effective filing date of the instant application, Applicants knew of only two non-specific protein effectors of DNA MeTase, specifically 5-azacytidine and 5-azadeoxycytidine.

Therefore, other than 5-azacytidine and 5-azadeoxycytidine, Applicants were not in possession of any other protein effectors of DNA methyltransferase at the time the invention was filed. These species of protein effectors are not representative of the genus protein effectors of the claimed invention because the genus is highly variant, and further experimentation would be required in order to isolate other protein effectors of DNA MeTase.

Double Patenting

6. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1-3, 6, and 11-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 44 of copending Application No. 09/817,913. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method recited in claim 44 of 09/817,913 broadly encompasses the full scope of all claims in the instant application. Claim 44 of the copending application is drawn to a method comprising contacting a cell with at least two reagents selected

from the group consisting of an antisense oligonucleotide that inhibits a specific histone deacetylase isoform, a histone deacetylase small molecule inhibitor that inhibits a specific histone deacetylase isoforms, an antisense oligonucleotide that inhibits a DNA methyl-transferase, and a DNA methyltransferase small molecule inhibitor. It is clear that the method of the copending application recites a method that comprises contacting a cell with an antisense oligonucleotide that inhibits a DNA methyl-transferase, and a DNA methyltransferase small molecule inhibitor. The claims of the instant application differ from the claims of the copending application to the extent that they are specifically directed to a method comprising contacting a cell with an antisense oligonucleotide that inhibits a DNA methyl-transferase, and a DNA methyltransferase small molecule inhibitor, and the claims of the copending application also encompasses methods comprising the co-administration of an antisense oligonucleotide that inhibits a specific histone deacetylase isoform, a histone deacetylase small molecule inhibitor that inhibits a specific histone deacetylase isoforms. Therefore, since the methods recited in the claims of the instant application are clearly contemplated by the method recited in claim 44 of co-pending application 09/817,913, the claims of the instant application represent an obvious variation of claim 44 of the copending application.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3, 6, and 11-34 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, and 11-37 of copending Application No. 10/145,493. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application

broadly encompass the claims of the instant application. The claims of the copending application are broadly drawn to a method for inhibiting the expression of a gene in a cell, a method for treating a disease responsive to inhibition of a gene in a mammal, and a method for inhibiting tumor growth in a mammal, wherein said methods comprise contacting or administering an effective synergistic amount of an antisense oligonucleotide which inhibits expression of the gene, and an effective synergistic amount of a protein effector of a product of the gene. However, the claims of the instant application are limited to wherein the gene in said methods is the DNA methyltransferase gene. This difference between the claims of the instant application and the copending application represents an obvious variation of the claims set forth in the copending application, because multiple dependent claims of the copending application expressly recite wherein the target gene of the recited methods is a DNA methyltransferase, see for example copending claims 24, 26, 29, and 31-37.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Janet L. Epps-Ford, Ph.D. whose telephone number is 571-272-0757. The examiner can normally be reached on Monday-Saturday, Flex Schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Janet L. Epps-Ford, Ph.D.
Examiner
Art Unit 1635

JLE